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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/352,466	07/13/1999	VIRGINIA C BROUDY	A-195CDD	2305

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/09/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/352,466	BROUDY ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-44* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 7/8/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/352,466 is acceptable and a RCE has been established. Claims 26-44 are currently under prosecution. An action on the RCE follows.

2. Claims 1-20 and 22-25 are withdrawn from further consideration as being drawn to non-elected inventions.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains some NEW GROUNDS of rejection.

Specification

5. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate the current status of all applications. 08/255193 is now U.S. Patent 5,922,847 and 08/011,078 is now U.S. Patent 5,489,516, and 07/681245 is abandoned.

b. The specification needs to be updated to indicate the current status of all co-pending applications, for example, page 1, lines 15-17, for example application 07/589701 is abandoned.

c. The ATCC number needs to be added to page 31, line 7.

d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Response to Arguments

6. The rejection of newly added claims 26-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

This rejection was originally for claim 21 and applies to claim 26 which recites "modifying sensitivity to cell cycle-specific chemotherapeutic agents" because the exact meaning of the phrase is not clear. It is not clear what "modifying" is meant to encompass or what is being modified . In addition, does the method increase the sensitivity or decrease the sensitivity?. Moreover, it is unclear what compounds are encompassed by "cell cycle-specific chemotherapeutic agents" because the specification lacks a clear definition of this phrase.

The response filed 7/8/02 has been carefully considured but is deemed not to be persuasive. The response states the rejection is moot in view of the cancellation of claim 21 and the arguments set forth in the after final amendment of 5/6/02. in response to this argument, the amendment after final was not entered, however, in order to have compact prosecution the amendment will be addressed. The response

states that one skilled in the art would understand what compounds are encompassed by "cell cycle-specific chemotherapeutic agents" namely "those chemotherapeutic agents which are specific for targets involved in cell division" (see page 3 of response of 5/6/02). In response to this argument, it is still unclear what compounds are encompassed as well as what is being modified and whether the method decreases or increased the sensitivity.

7. The rejection of newly added claims 26-44 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained and made again.

The rejection is reiterated and expanded for newly added claims 26-44.

Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification teaches an antibody which inhibits the binding of an SCF molecule to an SCF receptor, specifically one antibody designated SR-1 (see page 7, lines 1-2 and page 13, lines 11-15). The specification only mentions a method for modifying sensitivity to cell cycle-specific chemotherapeutic agent comprising administering an SCF-inhibiting amount of a monoclonal antibody (see pages 20-21). The specification fails to teach how to perform the method and complete method steps. The specification also does not enable the epitope to which the antibody produced from the hybridoma cell line ATCC No. HB 10716 binds Thus, undue experimentation would be required to perform the claimed method.

Further, the disclosure does not provide working examples wherein all of the steps required to practice the method are employed. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as cancer. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that skilled artisan is presented with a multitude of un-linked alternatives with no guidance as to which will enable use of the invention as claimed. Among these are (I) what sensitivity is modified, (ii) what specific cell cycle-specific chemotherapeutic agents to select, (iii) what cells to target or select, (iv) which of many diseases to select.

The specification has not demonstrated the reproducible production of antibodies which have properties identical to SR-1. The production of a hybridoma which secretes

a monoclonal antibody having a particular set of specifically defined characteristics is an unpredictable event. Given that a single example of the isolation of an antibody having the claimed properties has been presented herein, it is not clear that the isolation of the SR-1 antibodies did not merely represent a fortuitous event. In view of the lack of predictability of isolating further antibodies which are functionally equivalent to SR-1 together with the lack of exemplary material presented herein, it appears that undue experimentation would be required of one of skill in the art to practice the invention as claimed using the technology of the specification alone.

The specification fails to set forth the reproducibility of the generically claim monoclonal antibodies which bind to a human stem cell factor and have the claimed properties. In view of the unpredictability of producing antibodies having the claimed properties from among the 10^6- 10^{10} possible antibody variable region specificities encoded in the mammalian genome and in view of the lack of disclosure of the reproducibility of these antibodies, it does not appear that the antibodies required for the broadly claimed methods can be reproduced form he written disclosure alone. In addition, the specification discloses that the prior art was unable to produce an antibody to the c-kit receptor that would block the binding of the c-kit ligand SCF (see page 2, lines14-19) and the prior art antibodies that bound to c-kit did not block binding to the receptor. Thus, it appears that the only antibody with the claimed properties is the SR-1 antibody.

Therefore, a reasonable doubt exists as to whether the isolation of the monoclonal antibody may have been fortuitous and not reproducible without undue

experimentation. Filing of evidence of the reproducibility of the claimed monoclonal antibody without undue experimentation coupled with evidence of the public availability of the starting materials necessary to produce the claimed antibody is accordingly required.

Claim 27 recites an antibody that binds to an epitope recognized by the antibody produced by the hybridoma ATCC HB 10716. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Therefore, due the unpredictability in the art as evidenced from Greenspan et al and in view of the insufficient guidance and/or working examples concerning the use the claimed antibodies in a method of modifying sensitivity, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer antibodies for modifying sensitivity to cell cycle-specific chemotherapeutic agents without undue experimentation.

The response filed 7/8/02 has been carefully considured but is deemed not to be persuasive. The response states that for the reasons set forth in Applicant's amendment after final dated 5/6/02, it is believed that the rejection may be properly withdrawn (see page 5 of response of 7/8/02). In response to this argument, the amendment after final was not entered, however, in order to have compact prosecution the amendment will be addressed. The response filed 5/6/02 states "The claimed method is enabled in view of the teachings in the specification of an antibody which binds an epitope on a receptor recognized by human stem cell factor such that binding of stem cell factor is inhibited" and "With this antibody in hand, one skilled in the art would be able to carry out the steps of administering the antibody with undue experimentation" (see page 3 of response of 5/6/02). In response to these arguments, While the specification may enable an antibody that binds to the c-kit and inhibits binding to SCF, the method encompasses antibodies which bind to any receptor recognized by human stem cell factor and the specification only discloses an antibody to c-kit with the claimed properties. In addition, the response seems to indicate that if one had the SR-1 antibody in hand, which is the only antibody disclosed in the

specification, one would be able to carry out the steps of administering the antibody. While administration of the antibody would not be undue, one would need the SR-1 antibody and as mentioned above this antibody seems to be the only antibody that has the claimed properties. The response also states that the examiners argument that cancer therapy is unpredictable is not relevant since the claims are not directed to treating cancer. In response to this argument, the claims are broadly drawn to cancer where the agents are chemotherapeutic.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

8. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 32 is indefinite for reciting "essentially entirely" because the exact meaning of the phrase is not clear. Does the antibody inhibit binding or not?

9. Claims 27-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of SR-1 which is produced by hybridoma ATCC No. HB 10716 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species produced by the hybridoma ATCC No. HB 10716. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant's referral to the deposit of SR-1 as ATCC No. HB 10716 on page 13 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703)

306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879